

# Anti-tumour necrosis factor biological therapies for the treatment of uveitic macular oedema (UMO) for noninfectious uveitis

Tallouzi, Mohammad; Barry, Robert; Murray, Philip J; Calvert, Melanie; Moore, David; Denniston, Alastair

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## **Anti-tumour necrosis factor biological therapies for the treatment of uveitic macular oedema (UMO) for non-infectious uveitis (Protocol)**

Tallouzi MO, Barry RJ, Bucknall N, Mathers JM, Murray PI, Calvert MJ, Moore DJ, Denniston AK

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# Anti-tumour necrosis factor biological therapies for the treatment of uveitic macular oedema (UMO) for non-infectious uveitis

Mohammad O Tallouzi<sup>1</sup>, Robert J Barry<sup>2</sup>, Nick Bucknall<sup>3</sup>, Jonathan M Mathers<sup>1</sup>, Philip I Murray<sup>4</sup>, Melanie J Calvert<sup>1</sup>, David J Moore<sup>1</sup>, Alastair K Denniston<sup>5</sup>

<sup>1</sup>Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK.

<sup>2</sup>Institute of Immunology and Immunotherapy, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK.

<sup>3</sup>Shrewsbury, UK. <sup>4</sup>Academic Unit of Ophthalmology, Institute of Inflammation and Ageing, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK. <sup>5</sup>Department of Ophthalmology, Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

Contact address: Mohammad O Tallouzi, Institute of Applied Health Research, College of Medical and Dental Sciences, University of Birmingham, Birmingham, B15 2TT, UK. [mohd.tallouzi@nhs.net](mailto:mohd.tallouzi@nhs.net), [mxt500@bham.ac.uk](mailto:mxt500@bham.ac.uk).

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## ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of anti-TNF therapy for UMO.

## BACKGROUND

### Description of the condition

Uveitis describes a group of disorders characterised by intraocular inflammation. Uveitis is the fifth most common cause of visual loss in high-income countries, accounting for approximately 10% to 15% of total blindness (Durrani 2004; William 2007). This figure rises to 25% in low- and middle-income countries (Abdulaal 2015; Rao 2013). Although uveitis may affect any age group, it peaks in the working age population, with no significant difference between sexes (Acharya 2013). The annual incidence of uveitis is

estimated at 17.4 to 52.4 per 100,000 people with a prevalence of around 38 to 114.5 per 100,000 general population (Durrani 2004; Gritz 2004; Suhler 2008; William 2007).

Uveitis often occurs in younger people in the working population compared to other eye diseases such as cataracts and age-related macular degeneration, so the condition has a huge impact in terms of years of potential blindness and economic cost (Durrani 2004). Uveitis may be classified anatomically as anterior uveitis, intermediate uveitis, posterior uveitis or pan-uveitis (Bloch-Michel 1987; Deschenes 2008). It may arise from a range of different infectious and non-infectious aetiological sources. The focus of this review is non-infectious uveitis, most of which is thought to be autoimmune (or at least auto-inflammatory) and usually requires im-

munosuppressive treatment (Barry 2014; Van Gelder 1999). Non-infectious uveitis may be associated with a range of inflammatory syndromes, including ankylosing spondylitis, Behcet's disease, sarcoidosis and multiple sclerosis (Lee 2014a; Lee 2014b; Takeuchi 2013).

The leading cause of sight loss in people with uveitis is macular oedema, known in this context as uveitic macular oedema (UMO) (Durrani 2004; Lardenoye 2006). Macular oedema (MO) describes the accumulation of fluid in the retina (the light-sensitive inner lining of the eye) in the area that provides central vision known as the 'macula' (Davis 2010; De Smet 2010). MO is more common in forms of uveitis affecting the more posterior structures in the eye, namely intermediate and posterior uveitis and pan-uveitis; collectively these are sometimes referred to as posterior segment-involving uveitis. MO can also occur in association with anterior uveitis (Kaiser 2009).

Macular oedema accounts for 41% of visual impairment and 29% of blindness in uveitis (Levin 2014; Rothova 1996). The impact of UMO on visual acuity is usually assessed using standard distance visual acuity charts, either a Snellen chart or an Early Treatment Diabetic Retinopathy Study (ETDRS) chart. Acuties from Snellen charts are usually reported in metres in the UK and feet in the USA. Acuties from ETDRS charts are usually reported either as 'number of letters read' or converted into a LogMAR fraction. Although certain visual acuties are considered to be equivalent (e.g. 0.0 LogMAR = 6/6 UK Snellen = 20/20 US Snellen), these equivalences are approximate due to intrinsic differences between the charts (Kaiser 2009). Although the Snellen chart is still widely used in clinical practice, most trials use ETDRS charts due to various methodological advantages. Traditionally, MO has been assessed clinically using stereoscopic slit-lamp fundus biomicroscopy and fluorescein angiography, an invasive procedure requiring intravenous dye and stereo photography imaging testing (Brown 2004). More recently a non-invasive imaging technique, optical coherence tomography (OCT), has become a standard clinical practice in monitoring treatment response and follow-up of UMO (Karim 2013; Reinthal 2004). OCT may be more sensitive than clinical measures in detecting the presence of UMO and provides accurate measures of the structural changes in terms of macular thickness (Kempner 2013).

## Description of the intervention

There are a wide range of pharmacological treatments for UMO. Corticosteroids are the mainstay of acute treatment (Davis 2010), with alternative routes of administration including: systemic (oral, intravenous and intramuscular); local, which includes periocular injection (sub-Tenon and orbital floor injection); and intraocular (intravitreal injection or implant) (Kok 2005; Venkatesh 2008). For long-term treatment it is important to reduce corticosteroid usage, leading to the use of 'second-line' therapies, which are typically immunomodulatory and include T-cell in-

hibitors (e.g. ciclosporine, and tacrolimus) and anti-metabolites (e.g. azathioprine, methotrexate, mycophenolate mofetil). Alkylating agents (e.g. cyclophosphamide) have traditionally been used as a 'third line' for severe refractory disease (Barry 2014; Deuter 2009; Markomichelakis 2004; Neri 2008; Taylor 2009). Anti-vascular endothelial growth factor (VEGF) agents and oral carbonic anhydrase inhibitor (acetazolamide) have also occasionally been used to treat UMO (Karim 2013). Anti-tumour necrosis factor (anti-TNF) drugs (the subject of this review) are not licensed for the treatment of uveitis (a feature they share with almost all treatments for uveitis) but are commonly used off-licence - after the failure of one or more second-line agents, but before the use of an alkylating agent (Sharma 2009).

Anti-TNF drugs are biological agents that selectively block the actions of TNF, a critical cell signalling molecule ('cytokine') in the inflammatory process (Deuter 2009; McCluskey 2000). Originally pioneered in the 1990s for use in rheumatoid arthritis (RA), anti-TNF drugs are now central to the treatment of many inflammatory diseases including RA, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis (AS), Crohn's disease (Sharma 2009), and Behcet's disease (Hatemi 2008). As noted earlier, most non-infectious uveitis is immune mediated and is commonly associated with many of these same systemic diseases (Lee 2014a; Lee 2014b; Murphy 2004; Takeuchi 2013).

There are currently five anti-TNF agents licensed for a range of non-ocular inflammatory diseases; none are licensed for ocular inflammation (Scallan 1995; Scallan 2002). The first anti-TNF agent to be developed for clinical use was infliximab, a chimeric IgG1 that binds to soluble and membrane TNF- $\alpha$ , preventing TNF- $\alpha$  from binding to its receptor in the cell (Wooley 1995). The main route of administration is intravenous (Markomichelakis 2004). The second anti-TNF agent to reach clinical usage was etanercept. This is a soluble protein linked to the human Fc fragment of IgG1 that prevents TNF- $\alpha$  and  $\beta$  from interacting with their receptor; its route of administration is subcutaneous (Jabs 2001). The third anti-TNF drug is adalimumab, which is a humanised IgG monoclonal antibody that binds to human TNF- $\alpha$  (Kaymakçalan 2009). Adalimumab is administered subcutaneously (Rudwaleit 2009). In addition to direct effects on the TNF-pathways, downstream effects appear to include an increase of regulatory T cells and modulation of vascular endothelial growth factor (VEGF)-mediated pathways (Erckens 2011).

Golimumab is a human monoclonal antibody to TNF- $\alpha$  with the advantage of requiring only monthly subcutaneous injection (Cordero-Coma 2015; Feaz 2014; Miserocchi 2014). Certolizumab consists only of the pegylated humanised Fab fragment of a monoclonal antibody directed against TNF- $\alpha$ . It is administered subcutaneously once every two weeks (Sánchez-Cano 2013; Tluczek 2012). Both agents have shown benefits for ocular inflammatory disease; however, existing data are limited to case reports and case series (Mesquida 2013).

Although patients with uveitis have received treatment with other

anti-TNF drugs, the most commonly used anti-TNF agents are the monoclonal antibodies infliximab and adalimumab; in addition to the standard systemic administration, some authors have reported intravitreal administration (Pascual-Camps 2014; Schaap-Fogler 2014). Some patients with uveitis have also received other anti-TNF drugs for uveitis.

## How the intervention might work

The pathogenesis of the UMO is related to the underlying ocular inflammatory process (uveitis) causing release of inflammatory mediators including interleukin (IL)-1, IL-2, IL-6, IL-8, and TNF- $\alpha$ , transforming growth factor (TGF)- $\beta$  and interferon (IFN)- $\gamma$ , many of which directly or indirectly contribute to disruption of the blood-retina barrier. As a result, protein and large molecules are trapped within the retina, causing fluid flow out of the vessels via the osmotic gradient (Curnow 2006; Van Kooij 2006).

TNF- $\alpha$ , a key pro-inflammatory cytokine in a range of inflammatory conditions, has proven pivotal in animal models of uveitis and is present in intraocular fluids in human uveitis (Foxman 2002; Murphy 2004). It is a pleiotropic cytokine produced by a number of cells and has an important role in a range of leukocyte functions (Feldmann 2005; Sfikakis 2004). Specific roles include: increasing leukocyte recruitment to the eye via induction of chemokines and increased leukocyte adhesion to vascular endothelium; dendritic cell maturation to increase the effectiveness of their antigen presentation and cytokine production; macrophage activation and enhancing T-cell activation. TNF- $\alpha$  may also be pro-apoptotic for both infiltrating and resident cells (Cordero-Coma 2015). The exact cascade of inflammatory mediators that leads to UMO is not well understood (Curnow 2006; Schaap-Fogler 2014); however, there is agreement that TNF- $\alpha$  upregulates VEGF production in choroidal endothelial cells, and TNF- $\alpha$  blockade is associated with a reduction in serum VEGF levels (Calleja 2012; Giraudo 1998; Hangai 2006).

## Why it is important to do this review

UMO is the leading cause of sight loss in uveitis and a major cause of blindness in the working-age population. There is mechanistic data to support the proposal that anti-TNF drugs may provide more targeted disease control of uveitis than provided by current non-biological therapies, and there is evidence demonstrating significant benefit of anti-TNF drugs in related systemic inflammatory conditions. Off-licence use of anti-TNF agents for uveitis has become common in some centres, but there is a lack of national guidelines or consensus statements and considerable variation in practice (Davis 2010; Karim 2013; Sreekantam 2011). This review will assess the effects of the anti-TNF therapy in the management of UMO. It is timely to review the literature in order to evaluate

and summarise the available evidence for anti-TNF therapy used for the treatment of UMO, which may form the basis of evidence-based clinical recommendations.

## OBJECTIVES

To assess the effects of anti-TNF therapy for UMO.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We will include all relevant randomised controlled trials (RCTs) assessing anti-TNF therapy for treating UMO.

#### Types of participants

We will include trials with participants of any age, sex or ethnicity with a diagnosis of UMO.

#### Types of interventions

The primary comparisons of this review will be:

- anti-TNF versus no treatment or placebo;
- anti-TNF versus another pharmacological agent;
- comparison of different anti-TNF drugs;
- comparison of different doses and routes of administration of the same anti-TNF drug.

#### Types of outcome measures

We will not select studies based on outcomes. However, we do consider clinical and patient-reported outcomes to be important for the aims of the review. We will classify outcomes as primary and secondary as follows.

#### Primary outcomes

The primary outcome measure for this review will be best corrected visual acuity (BCVA) in the treated eye. This will be measured in the following ways.

- Mean change in LogMAR BCVA between baseline (before treatment) and at the pre-specified time points.
- The proportion of participants gaining 5 or more ETDRS letters (equivalent to 1 ETDRS line or 0.1 LogMAR

improvement) at the follow-up visit in the treated eye at the pre-specified time point.

- The proportion of participants losing 5 or more ETDRS letters (equivalent to 1 ETDRS line or 0.1 LogMAR worsening) recorded at the follow-up visit in the treated eye at the pre-specified time point.

## Secondary outcomes

### *Anatomical macular change*

We will record anatomical changes in macular structure as studies measured them.

- Mean change in central macular thickness (CMT) in microns, as assessed by optical coherence tomography (OCT) at pre-specified time points.
- Proportion with clinical resolution of UMO, as assessed by stereoscopic slit-lamp fundus biomicroscopy (clinical) at pre-specified time points.
- Proportion with angiographic resolution of UMO, as assessed by fundus fluorescein angiography at pre-specified time points.

### *Clinical estimation of vitreous haze*

- Changes in vitreous haze, as assessed by stereoscopic fundus indirect biomicroscopy examination at pre-specified time points.

### *Health-related quality of life*

- Mean change in quality of life score (both vision-related and non-vision related), as measured by any validated quality of life questionnaire at the pre-specified time points

## Adverse events

- We will record all adverse events reported in the included studies at the pre-specified time points.

We expect that data will be available at multiple time points within and between studies. We will categorise nominal data from each analysis into three groups. We will group the postintervention time points for assessment of outcomes into three different time ranges: 3 months or less, more than 3 and up to 6 months, and more than 6 months.

## Search methods for identification of studies

### Electronic searches

The Cochrane Eyes and Vision Information Specialist will search the following electronic databases for randomised controlled trials

and controlled clinical trials. There will be no language or publication year restrictions.

- Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (latest issue) ([Appendix 1](#));
- MEDLINE Ovid (1946 to present) ([Appendix 2](#));
- Embase Ovid (1947 to present) ([Appendix 3](#));
- Web of Science Conference Proceedings Citation Index-Science (CPCI-S) (1970 to present) ([Appendix 4](#));
- System for Information on Grey Literature in Europe (OpenGrey) (1995 to present) ([Appendix 5](#));
- ISRCTN registry ([www.isrctn.com/editAdvancedSearch](http://www.isrctn.com/editAdvancedSearch)) ([Appendix 6](#));
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)) ([Appendix 7](#));
- World Health Organization International Clinical Trials Registry Platform ([www.who.int/ictpr](http://www.who.int/ictpr)) ([Appendix 8](#));

### Searching other resources

We will search the reference lists of potentially relevant studies to identify any additional trials. We will not handsearch conference proceedings or journals for this review.

## Data collection and analysis

### Selection of studies

We will carry out the study selection process in two stages.

- First, we will screen the title and the abstract of identified articles in order to remove irrelevant records, excluding articles that obviously do not meet the selection criteria.
- Secondly, we will retrieve the full-text of any potentially relevant articles and assess them against the selection criteria.

At both stages, two review authors (MT and RB) will independently assess articles, resolving any disagreements by discussion and if required referral to a third review author (DM). Two review authors will independently screen the titles and abstracts resulting from the searches using web-based software ([Covidence 2016](#)). We will illustrate the study selection processes using a PRISMA flow diagram (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) ([Moher 2010](#)). We will have non-English language articles translated in part or in full to aid study selection and analysis.

### Data extraction and management

See: [Appendix 9](#).

Two review authors (MT and RB) will extract data independently using an online data extraction form in Covidence ([Covidence](#)



2016). We will resolve any discrepancies through discussion and referral to a third review author (DM) if needed. We will use a standardised piloted data extraction form. We may contact study authors for further information. We will enter all data into Review Manager 5 software (RevMan 2014). For each study, we will extract at least the following information.

1. Study characteristics.
  - i) Authors, publication year, title and journal.
  - ii) Study design.
  - iii) Setting.
  - iv) Sample size.
  - v) Length of follow-up.
  - vi) Analysis.
2. Participant characteristics.
  - i) Selection/recruitment criteria.
  - ii) Demographic data; number, age, sex, socioeconomic status and ethnicity.
  - iii) Type of uveitis (anatomical categorisation, syndrome/aetiological classification).
  - iv) Comorbidity.
  - v) Co-medication.
3. Intervention and comparator.
  - i) Pharmacological agents.
  - ii) Regimen (dose, frequency of administration, route of administration).
  - iii) Comparator details.
  - iv) Any difference in underlying care between treatment group.
4. Outcomes and findings.
  - i) Outcomes measured and results for each outcome including precision and statistical test results.
  - ii) Completeness of follow-up for each outcome.

### Assessment of risk of bias in included studies

Two review authors will independently assess the quality of included studies, resolving disagreements through discussion and referral to a third review author (DM) if required. We will employ the methods set out in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Intervention* (Higgins 2011).

We will consider the following domains.

- Selection bias: allocation concealment bias, randomisation sequence generation bias.
- Performance bias: masking (or blinding) of study participants and the researcher.
- Detection bias: masking (or blinding) of outcome assessors.
- Attrition bias: loss to follow-up and rate of compliance in both groups (withdrawals from the study lead to incomplete outcome data).
- Reporting bias: selective outcome reporting.

We will report the risk of bias domains as being at low risk, high risk or unclear risk (lack of information or uncertainty of potential

bias) (Higgins 2011). We will add data from the included studies on risk of bias into RevMan 2014.

### Measures of treatment effect

#### Continuous data

We will report continuous variables as mean differences with their corresponding 95% confidence intervals.

#### Dichotomous data

We will report dichotomous variables as risk ratios (RRs) with their corresponding 95% confidence intervals.

We are likely to present results for some outcomes using a number of different measures/statistics measured within and between studies. For example, studies might report visual acuity in metres or feet (from Snellen charts), a LogMAR score, or number of letters or lines read (from ETDRS charts). Investigators may report the change in acuity as a change in any one of these indices or categorised against a threshold, for example, proportion of participants with change greater or equal to a specific number of lines/letters read (Kaiser 2009). Thus, different studies may consider visual acuity to be continuous data (e.g. group mean LogMAR score), discrete data (e.g. number of lines read) or dichotomous data (e.g. proportion of participants reading  $x$  lines, or proportion with a LogMAR score greater than  $y$ ). It is likely that continuous and dichotomous data will be most common. We will consider converting data between formats to maximise the data available for each analysis (for example, if authors state the type of chart, we might convert letters into lines; interchange LogMAR score and letters; and approximate Snellen UK, US and ETDRS data). We will undertake any conversion of data with due caution, taking into account known issues (Kaiser 2009). We will explicitly acknowledge the impact of any converted data on findings and explore this aspect through sensitivity analysis.

We will also analyse secondary outcome measures, presenting CMT as mean difference (MD) with 95% confidence intervals. We will pool health-related quality of life from the same scales using mean difference, and when studies use different scales to assess the same underlying concepts/domains, we will use standardised mean difference.

For adverse events reported in the included studies, we will record counts and rates. We may consider these data as continuous if the adverse events are common and occur often (presented as mean difference) or dichotomous data if the adverse events occur rarely (presented as rate ratio).

### Unit of analysis issues



Clinical trials in ophthalmology may randomise one or both eyes of participants to the intervention. The unit of randomisation may depend on the intervention.

- If the intervention is systemic (IV or SC) then the unit of randomisation in the studies will be the participant.
- If the intervention is intraocular - then the unit of randomisation could be the participant or the eye.

The unit of analysis might also depend on the outcome.

- For most outcomes related to vision, our primary unit of analysis will be the eye.
- For outcomes related to things like quality of life, the unit of analysis will be the participant.
- For adverse events, the unit of analysis will be the participant (and/or the eye in case of intraocular administration).

If studies include only one eye from each participant, the unit of analysis can either be the eye or the person. If two eyes from each participant receive the same intervention, and authors report them as a single unit (either through only one eye used in analysis, or as the average outcome for the two eyes), then the unit of analysis will be the participant.

If studies include two eyes per participant, with no differences in treatment between eyes, and they analyse them as two eyes, the outcome in each eye is likely to be more similar to the outcome in the companion eye than the eye of a different participant; therefore the study design could/should be considered as comparable to a cluster-randomised study.

If the intervention is intraocular administration, and participants receive different treatments in each eye (e.g. paired-eye/within-person design), we can compare outcomes between the two eyes and assess within-person differences if data are available. However, if the study includes more than one eye from some participants but not all participants, and the unit of analysis is the eye, then we should record this, as there are issues with unit of analysis that may not be resolvable. There is inadequate data available to know whether the intravitreal injection of anti-TNF agents may result in therapeutically significant systemic levels. On this basis, we will include any within-person (paired-eye) studies for intravitreal anti-TNF but report them separately.

### Dealing with missing data

We will assess all the included studies for number of participants excluded or lost to follow-up. For unclear or missing required information in study reports (e.g. on features such as study methods, outcome data, and measures of data variation), we will contact study authors. However, if the authors do not respond within four weeks or are not able to provide the additional data, we will conduct analyses based on the best available information. We will identify the distribution of missing data between the two arms and discuss the potential impact of missing data on the findings of the review.

### Assessment of heterogeneity

We will assess clinical and methodological heterogeneity to determine whether studies are sufficiently similar for each comparison/outcome to ensure that data pooling by meta-analysis is appropriate (Higgins 2002; Huedo-Medina 2006). If we combine studies in a meta-analysis, we will report the  $I^2$  statistic (which gives the percentage of the total variability in the data due to between-study heterogeneity) and the  $\text{Tau}^2$  statistic (which gives an estimate of the between-study variance), where appropriate (Higgins 2011).

### Assessment of reporting biases

We will examine selective outcome reporting by comparing outcomes reported in included studies and the outcomes recorded in study protocols. If the protocols are not publicly available, we will contact authors to supply them. For each meta-analysis containing 10 or more studies, we will construct a funnel plot and assess asymmetry in the plotted data (Peters 2008). Any asymmetry may imply possible publication bias, poor reporting of small studies, true heterogeneity or chance.

### Data synthesis

We will assess the consistency of clinical and methodological study characteristics, and if there is no substantial heterogeneity between the trials, we will combine results in a meta-analysis using a random-effects model. If there is substantial clinical or statistical heterogeneity, we will not combine study results in meta-analysis but will present data in a narrative summary.

### Subgroup analysis and investigation of heterogeneity

We will consider subgroup analysis for clinical and anatomical classification of uveitis (anterior, intermediate, posterior and pan) where deemed appropriate.

### Sensitivity analysis

We will perform sensitivity analysis to assess the robustness of the results and the effect of excluding trials judged to have a high risk of bias in one or more domains.

### Summary of findings table

If sufficient data are available, we will produce a 'Summary of findings' table for outcomes at six months' follow-up to provide key information concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on all of the primary and secondary outcomes for a given comparison. Two review authors will independently use the GRADE tool to assess the certainty of the evidence in the included studies

(GRADEpro 2014). We will resolve any discrepancies by discussion and refer to a third review author if needed. The table of results will include the primary outcome for the review which will be the best corrected visual acuity (BCVA) using either the mean change in LogMAR BCVA from baseline at the pre-specified time point or the proportion of participants gaining 5 or more ETDRS letters from baseline BCVA. In addition, the tables will include results for the following outcomes.

- Mean change in CMT from the baseline at the pre-specified time point.
- Proportion of eyes with absence of dye leakage on fluorescein angiography.
- Mean change in vitreous haze from the baseline.
- Mean change in quality of life score.

- Proportion of participants with adverse events.

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\* Indicates the major publication for the study

## APPENDICES

### Appendix I. CENTRAL search strategy

- #1 [mh "Macular Edema"]
- #2 [mh "Macula Lutea"]
- #3 macula\* near/3 oedema
- #4 macula\* near/3 edema
- #5 UMO
- #6 maculopath\*
- #7#1 or #2 or #3 or #4 or #5 or #6
- #8 [mh uveitis]
- #9 uveiti\*
- #10 iritis
- #11 iridocycliti\*
- #12 anterior near/2 scleriti\*
- #13 pars planitis
- #14 retinochoroidit\* or choroidit\*
- #15 Bechet\* or Vogt or Koyanagi or Harada or Fuch\*
- #16 [mh retinitis]
- #17 retinitis or neuroretinitis
- #18 uveoretinitis or uveo retinitis
- #19 vitritis or panuveitis or panophthalmiti\*

#20 ophthalm\* near/2 sympathetic  
 #21 [mh "arthritis juvenile rheumatoid"]  
 #22 juvenile near/2 rheumatoid near/2 arthriti\*  
 #23 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22  
 #24 [mh ^"Tumor Necrosis Factor-alpha"]  
 #25 [mh ^"Antibodies, Monoclonal"]  
 #26 [mh ^"Antibodies, Monoclonal, Humanized"]  
 #27 [mh Infliximab]  
 #28 [mh Adalimumab]  
 #29 [mh Etanercept]  
 #30 [mh ^"Certolizumab Pegol"]  
 #31 remicade\* or humira\* or enbrel\* or golimuab\* or simponi\* or cimzia\*  
 #32 #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31  
 #33 #7 and #23 and #32

## Appendix 2. MEDLINE Ovid search strategy

1. randomized controlled trial.pt.
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. (group or groups).ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. Macular Edema/
14. Macula Lutea/
15. (macula\$ adj3 oedema).tw.
16. (macula\$ adj3 edema).tw.
17. UMO.tw.
18. maculopath\$.tw.
19. or/13-18
20. exp uveitis/
21. uveiti\$.tw.
22. iritis.tw.
23. iridocycliti\$.tw.
24. (anterior adj2 scleriti\$.tw.
25. pars planitis.tw.
26. (retinochoroidit\$ or choroidit\$.tw.
27. (Bechet\$ or Vogt or Koyanagi or Harada or Fuch\$.tw.
28. exp retinitis/
29. (retinitis or neuroretinitis).tw.
30. (uveoretinitis or uveo retinitis).tw.
31. (vitritis or panuveitis or panophthalmiti\$.tw.
32. (ophthalm\$ adj2 sympathetic).tw.
33. arthritis juvenile rheumatoid/
34. (juvenile adj2 rheumatoid adj2 arthriti\$.tw.
35. or/20-34

36. Tumor Necrosis Factor-alpha/
37. Antibodies, Monoclonal/
38. Antibodies, Monoclonal, Humanized/
39. Infliximab/
40. Adalimumab/
41. Etanercept/
42. Certolizumab Pegol/
43. (remicade\$ or humira\$ or enbrel\$ or golimuab\$ or simponi\$ or cimzia\$).tw.
44. or/36-43
45. 19 and 35 and 44
46. 12 and 45

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by [Glanville 2006](#)

### Appendix 3. Embase Ovid search strategy

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random\$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
13. (clin\$ adj3 trial\$).tw.
14. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).tw.
15. exp placebo/
16. placebo\$.tw.
17. random\$.tw.
18. exp experimental design/
19. exp crossover procedure/
20. exp control group/
21. exp latin square design/
22. or/12-21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/
27. exp prospective study/
28. (control\$ or prospectiv\$ or volunteer\$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. exp retina macula edema/
34. eye edema/
35. (macula\$ adj3 oedema).tw.
36. (macula\$ adj3 edema).tw.
37. UMO.tw.



38. maculopath\$.tw.
39. or/33-38
40. exp eye inflammation/
41. uveiti\$.tw.
42. iritis.tw.
43. iridocycliti\$.tw.
44. (anterior adj2 scleriti\$).tw.
45. pars planitis.tw.
46. (retinochoroidit\$ or choroidit\$).tw.
47. (Bechet\$ or Vogt or Koyanagi or Harada or Fuch\$).tw.
48. (retinitis or neuroretinitis).tw.
49. (uveoretinitis or uveo retinitis).tw.
50. (vitritis or panuveitis or panophthalmiti\$).tw.
51. (ophthalm\$ adj2 sympathetic).tw.
52. arthritis juvenile rheumatoid/
53. (juvenile adj2 rheumatoid adj2 arthriti\$).tw.
54. or/40-53
55. exp tumor necrosis factor alpha/
56. antibodies, monoclonal, humanized/
57. monoclonal antibody/
58. Infliximab/
59. Adalimumab/
60. Etanercept/
61. Certolizumab Pegol/
62. (remicade\$ or humira\$ or enbrel\$ or golimuab\$ or simponi\$ or cimzia\$).tw.
63. or/55-62
64. 39 and 54 and 63
65. 32 and 64

#### **Appendix 4. Web of Science CPCI search strategy**

- #10 #9 AND #8 AND #3
- #9 TS=(Infliximab OR Adalimumab OR Etanercept OR Certolizumab NEAR/1 Pegol OR remicade\* OR humira\* OR enbrel\* OR golimuab\* OR simponi\* OR cimzia\*)
- #8 #4 OR #5 OR #6 OR #7
- #7 TS=(vitritis OR panuveitis OR panophthalmiti\* OR ophthalm\* NEAR/2 sympathetic OR juvenile NEAR/2 rheumatoid NEAR/2 arthriti\*)
- #6 TS=(retinochoroidit\* OR choroidit\* OR Bechet\* OR Vogt OR Koyanagi OR Harada OR Fuch\* OR retinitis OR neuroretinitis OR uveoretinitis OR uveo NEAR/1 retinitis)
- #5 TS=(pars NEAR/1 planitis OR anterior NEAR/2 scleriti\*)
- #4 TS=(uveiti\* OR iritis OR iridocycliti\*)
- #3 #1 OR #2
- #2 TS=(UMO OR maculopath\*)
- #1 TS=(macula\* NEAR/3 oedema OR macula\* NEAR/3 edema OR macula\* NEAR/3 lutea)

## Appendix 5. OpenGrey search strategy

(macular oedema OR uveitis) AND (infliximab OR adalimumab OR etanercept OR golimumab OR certolizumab)

## Appendix 6. ISRCTN search strategy

“( Condition: macular oedema OR uveitis AND Interventions: infliximab OR adalimumab OR etanercept OR golimumab OR certolizumab )”

## Appendix 7. ClinicalTrials.gov search strategy

macula edema OR uveitis | (infliximab OR adalimumab OR etanercept OR golimumab OR certolizumab)

## Appendix 8. ICTRP search strategy

macular oedema OR uveitis = CONDITION AND infliximab OR adalimumab OR etanercept OR golimumab OR certolizumab = INTERVENTION

## Appendix 9. Data on study characteristics

Mandatory items		Optional items
Methods		
Study design	<ul style="list-style-type: none"><li>· <b>Parallel group RCT</b> <i>i.e. people randomised to treatment</i></li><li>· <b>Within-person RCT</b> <i>i.e. eyes randomised to treatment</i></li><li>· <b>Cluster RCT</b> <i>i.e. communities randomised to treatment</i></li><li>· <b>Cross-over RCT</b></li><li>· Other, specify</li></ul>	<ul style="list-style-type: none"><li>Exclusions after randomisation</li><li>Losses to follow up</li><li>Number randomised/analysed</li><li>How were missing data handled? <i>e.g., available case analysis, imputation methods</i></li><li>Reported power calculation (Y/N), <i>if yes, sample size and power</i></li><li>Unusual study design/issues</li></ul>
Eyes or Unit of randomisation/ unit of analysis	<ul style="list-style-type: none"><li>· <b>One eye included in study, specify how eye selected</b></li><li>· <b>Two eyes included in study, both eyes received same treatment, briefly specify how analysed (best/worst/average/both and adjusted for within person correlation/both and not adjusted for within person correlation) and specify if mixture one eye and two eye</b></li><li>· <b>Two eyes included in study, eyes received different treatments, specify if correct pair-matched analysis done</b></li></ul>	
Participants		

(Continued)

Country		Setting
Total number of participants	<i>This information should be collected for total study population recruited into the study. If these data are only reported for the people who were followed up only, please indicate.</i>	Ethnic group
Number (%) of men and women		Equivalence of baseline characteristics (Y/N)
Average age and age range		Number (%) of men and women
Inclusion criteria		Average age and age range
Exclusion criteria		
<b>Interventions</b>		
Intervention (n= ) Comparator (n= ) <b>See MECIR 65 and 70</b>	<ul style="list-style-type: none"> <li>· Number of people randomised to this group</li> <li>· Drug (or intervention) name</li> <li>· Dose</li> <li>· Frequency</li> <li>· Route of administration</li> </ul>	
<b>Outcomes</b>		
Primary and secondary outcomes <i>as defined in study reports</i> <b>See MECIR R70</b>	List outcomes Adverse events reported (Y/N) Length of follow up and intervals at which outcomes assessed	Planned/actual length of follow up
<b>Notes</b>		
Date conducted	Specify dates of recruitment of participants mm/yr to mm/yr	Full study name: <i>(if applicable)</i> Reported subgroup analyses (Y/N) Were trial investigators contacted?
Sources of funding		
Declaration of interest <b>See MECIR 69</b>		

## CONTRIBUTIONS OF AUTHORS

MT drafted the manuscript. MT, AD, DM, RB and MC led the development of the protocol. AD, RB and PM provided clinical advice; DM and MC provided methodological advice. NB provided the patient public perspective. JM has given input in reviewing protocol. All authors read and approved the final manuscript.

## DECLARATIONS OF INTEREST

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